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Electrochemical Detection of the Neurotransmitter Dopamine by Nanoimprinted Sub-µm Microelectrodes and CMOS Circuitry with near 100% Collection Efficiency

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Abstract

The sub-µm interdigitated microelectrodes presented in this work aims at achieving a high collection efficiency for electrochemical dopamine (DA) detection. Through nanoimprint technology, sub-µm microelectrodes can be batch fabricated without relying on the expensive electron-beam lithography repeatedly. The applied reduction and oxidation potentials are determined by cyclic voltammetry at -0.2 V and 0.6 V. The effectiveness of nanoimprinted electrodes is clearly illustrated by the small deviations of produced electrochemical currents with respect to analytic values. The sensitivities are 2.89 and 1.73 nA/µM for interdigitated microelectrodes with gaps of 300 and 600 nm. The average collection efficacy values are 97.9% and 95.4%, respectively. Signal transduction is achieved by a CMOS sensing circuit. The detectable resolution is about 0.1 µM.

Keywords: CMOS; capacitive; ultrasound; transducer.

1. Introduction

Parkinson's disease is a degenerative disease of the nervous system associated with trembling of the arms and legs, stiffness and rigidity of the muscles and slowness of movement. Until now, in humans, a deficiency of the neurotransmitter dopamine in the basal ganglia of the brain has been known well to play a critical role in Parkinson's disease. Dopamine acts like a brain chemical to transmit messages to parts of the brain for coordination of body movements. Medications or surgery can provide relief from the symptoms. Deep brain stimulation is presently the most used surgical means of treatment. Gene therapy and implantation of stem cells are among the methods under evaluation. The long-term goal of this research is to develop a miniaturized, implantable dopamine sensor capable of providing real-time and localized detection of dopamine concentration in a patient’s brain, allowing convenient monitoring of a patient’s progress after surgery. Interdigitated microelectrodes have been widely adopted to study electrochemical reaction of various electroactive species for quantitative analysis. The main advantage, as the width and gap of the microelectrodes are reduced by microfabrication, is the achieved high sensitivity due to the enhanced redox current and redox cycles. The improved signal-to-noise ratio has made them suitable for use as electrochemical detectors in high-performance liquid chromatography (HPLC) and electrophoresis. Interdigitated

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microelectrodes can be used as enzyme immunoassays for rapid testing of a variety of clinical analytes. The sub-μm interdigitated microelectrodes presented in this work aims at achieving a high collection efficiency for electrochemical dopamine detection. Signal transduction is conveniently achieved by a CMOS sensing circuit.

2. Device fabrication and design

Fabrication of the nanoimprint stamps is described as follows. The silicon wafer was coated with 300-nm photoresist (PMMA 50K) and the sub-μm electrode patterns were transferred with an electron-beam lithography system (Elionix ELS-7800). Exposed resist was developed afterward (Shipley developer MF319). Immediately after development, 20-nm thick Cr was thermally evaporated and lifted-off in acetone under ultrasonic agitation, followed by cleaning in sulfuric acid to remove particles. The sample was then transferred into the reactive ion-etching chamber to perform silicon etch of 300 nm with the CF_4 gas and Cr as the etch-resistant mask. The sample and the liquid F_{13}-TCS were placed into a chamber that was filled with nitrogen gas and heated to 270°C for 2 hours. Evaporated F_{13}-TCS reacted immediately to form a covalent linkage with the –OH bond on the stamp surface. A F_{13}-TCS monolayer was formed on the stamp surface as an anti-stiction layer. The subsequent electrode fabrication was performed on 4-in. <100> silicon wafers with a 500-nm PECVD silicon nitride layer. A double-layer photoresist comprising of 300-nm PMMA 950k A7 and 80-nm PMGI SF2 was employed in order to obtain a good lift-off profile afterward. The conditions for nanoimprint (by NX 2000, Nanonex Inc.) were: temperature = 150°C, pressure = 400 psi, imprint time =3 min., and release temperature = 50°C. After imprint, a reactive-ion etch was performed to remove the residual PMMA with O_2 plasma. The PMGI SF2 was developed in 2.38% TMAH for 10 seconds to make undercut for lift-off. Next, we deposited 5-nm Cr, as an adhesion layer, and 25-nm Au thin films and performed lift-off in warm TMAH with ultrasonic agitation to complete electrode fabrication. The leads and bond pads were made afterwards by conventional photolithography. Fig. 1 shows the fabricated device with a 300-nm gap.

Dopamine can be oxidized at the anode by producing two electrons and dopamine ortho-quinone, and reduced back at adjacent cathode when a proper reduction potential is given. The relationship between the produced redox current was studied by Aoki et al. [1]. The ratio of the produced cathodic current to the anodic current is defined as the collection efficiency, which depends on the electrode dimensions and the flow rate. High collection efficiency can be obtained when the gap between electrodes is in the same order as the diffusion layer thickness. The CMOS sensing circuit as shown in Fig. 2 is designed and fabricated by using a 0.35-μm CMOS process. The potential at the sensing node is regulated by use of a large external capacitor. The final output voltage is produced through a buffer circuit which is also made of the same operational amplifier. The produced oxidation current at the anode is amplified by the wide-swing cascade current mirror with a current gain of 10. The amplified current is then converted to a voltage by use of an integrating capacitor with a value of 4 pF. An external clock signal constantly resets the output and controls the integration time. The total circuit size is 370 μm × 280 μm. For an input current of 1 nA, the current mirror and the op-amp consume 36 nW and 0.9 mW, respectively.

3. Measurement

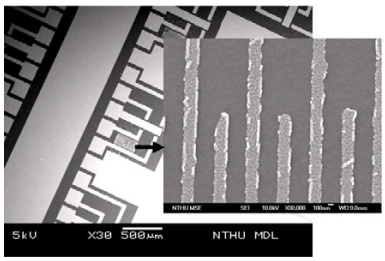

Fig. 1. SEM of the fabricated sub-μm interdigitated microelectrodes.

The electrochemical experiment was performed at room temperature (25°C) and atmospheric pressure. Cyclic voltammetry was performed using the fabricated microelectrodes to identify the respective oxidation and reduction potentials for dopamine (Sigma-Aldrich, USA) in phosphate buffer solution (pH=8.1, J. T. Baker, USA). Fig. 3 shows the measured result of 1-mM dopamine by using an electrochemical workstation (Model 701B, CH Instruments, Austin, TX) at a scan rate of 50 mV/sec. The curves show the current values become positive and negative when reduction and oxidation take place, respectively. One peak occurs at about -0.15 V and the other at about 0.5 V, both with respect to the Ag/AgCl reference electrode. The values near the two peaks can be used as the reduction and oxidation potentials. Electroactive functional groups presented on the electrode surface can also be oxidized or reduced, producing an additional background current that limits the minimum detectable concentration of the desired target. The other curve in the figure shows the electrochemical reaction of the buffer solution of 20 μM. The electrochemical experiment was performed at room temperature (25°C) and atmospheric pressure. Cyclic voltammetry was performed using the fabricated microelectrodes to identify the respective oxidation and reduction potentials for dopamine (Sigma-Aldrich, USA) in phosphate buffer solution (pH=8.1, J. T. Baker, USA). Fig. 3(a) shows the measured result of 1-mM dopamine by using an electrochemical workstation (Model 701B, CH Instruments, Austin, TX) at a scan rate of 50 mV/sec. The curves show the current values become positive and negative when reduction and oxidation take place, respectively. One peak occurs at about -0.15 V and the other at about 0.5 V, both with respect to the Ag/AgCl reference electrode. The values near the two peaks can be used as the reduction and oxidation potentials. Electroactive functional groups presented on the electrode surface can also be oxidized or reduced, producing an additional background current that limits the minimum detectable concentration of the desired target. The other curve in the figure shows the electrochemical reaction of the buffer solution of 20 μM. For the following experiments, the anode was held at 0.6 V and the cathode at -0.2 V with respect to the Ag/AgCl reference electrode. Dopamine solutions of concentrations from 0.5 μM to 8 μM (pH values between 6.5 and 6.8) were added to microelectrodes (gap = 300 nm; length = 170 μm; 150 pairs) and the produced reduction and oxidation currents were recorded by the electrochemical workstation as shown in Fig. 3(b). It took about a few hundred seconds for the responses to reach steady states. The long reaction time can be significantly reduced to few tenths of seconds by establishing a flow-cell setup that can confine the solution in a small cell volume at a fixed flow rate. Measured steady-state currents increased with DA concentrations with sensitivities of 2.89 and 1.73 nA/μM, respectively, for the 300-nm and 600-nm microelectrode designs. The result matched very well with respect to the analytic data as shown in Fig. 4(a). The average collection efficacy values were 97.9% and 95.4%, respectively, indicating that a small electrode separation enhanced the collection efficiency. For measurement with the CMOS circuit, phosphate buffer and 0.3, 0.5, and 1-μM dopamine solutions were injected on the 300-nm electrodes by a micro-pipette. Fig. 4(b) depicts the corresponding output waveforms from the CMOS circuit. The minimum detectable concentration can be at least as low as 0.1 μM.

4. Conclusion

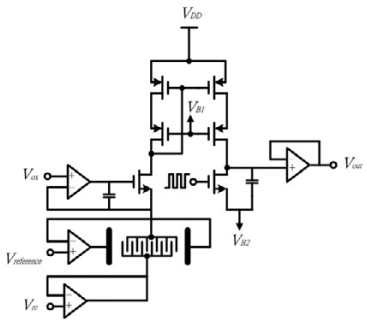

Fig. 2. Schematic of the CMOS circuitry for detection of produced electrochemical current.

This work presents the use of sub-μm interdigitated gold electrodes, made by the nanoimprint technology, with CMOS circuit for electrochemical detection of dopamine. The maximum collection efficiency can reach almost 98% at zero flow rate. The measured current values increase quite linearly with respect to the dopamine concentration, and matches well with respect to the calculated values. A flow-cell setup with flow-rate control can be used to improve the long diffusion time of the redox reaction by one to two orders of magnitude.

Acknowledgements

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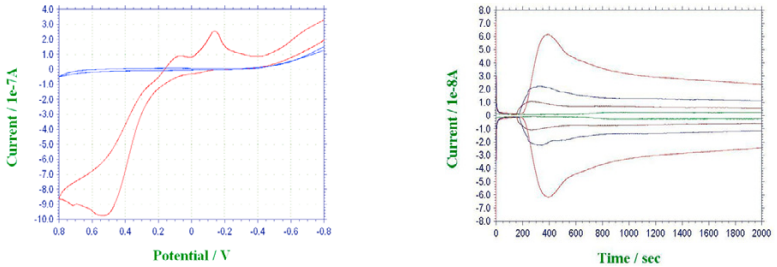
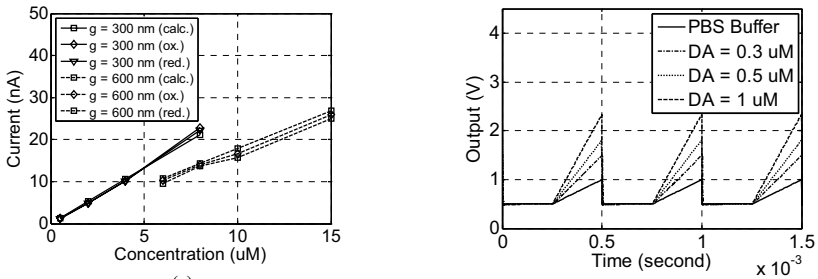


(a) (b)

Fig. 3. (a) Measured cyclic voltammograms of 1-mM dopamine and 20-μM buffer. (b) Measured current values with respect to time for dopamine concentrations from 2 μM to 30 μM.



(a) (b)

Fig. 4. (a) Measured and analytic redox currents with respect to DA concentrations for two sets of microelectrodes. (b) Measured output waveforms for DA concentrations from 0.3 to 1 μM (gap = 300 nm).